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## Consanguinity and Its Effect on Morbidity and Congenital Disorders Among Arabs in Israel

Sharkia Rajech<sup>1,2</sup>, Athamny Esmael<sup>1</sup>, Khatib Mohamad<sup>3</sup>, Sheikh-Muhammad Ahmad<sup>3</sup>, Azem Abdussalam<sup>4</sup> and Mahajnah Muhammad<sup>5</sup>

<sup>1</sup>The Triangle Regional Research and Development Center

<sup>2</sup>Beit-Berl Academic College

<sup>3</sup>The Galilee Society - The Arabs National Society for Research and Health Services

<sup>4</sup>Department of Biochemistry, Faculty of Life Sciences, Tel-Aviv University

<sup>5</sup>Child Development and Pediatric Center, Hillel Yaffe Medical Center, Affiliated with the Rappaport Faculty of Medicine, Technion, Haifa Israel

### 1. Introduction

Genetic diseases, especially autosomal recessive diseases, are rare in the general population. However, they become unusually frequent in certain communities worldwide as a result of genetic isolation due to social, geographic or religious factors. When a new mutation is inserted in such a population it spreads rapidly, leading to an increased prevalence of carriers and a large number of affected homozygous individuals. There are high frequencies of genetic diseases and congenital disorders among Arab populations (Tadmouri et al., 2009; Teebi & S.A. Teebi 2005). The high rates of genetic diseases and congenital disorders in the Arab populations can be attributed to several factors including: a) The high rate of traditional consanguineous marriages, which increases the frequency of autosomal recessive diseases; b) a relatively high birth rate of infants with chromosomal disorders related to advanced maternal age such as Down Syndrome and other trisomies; c) a relatively high birth rate of infants with malformations due to new dominant mutations related to advanced paternal age; d) large family sizes, which may increase the number of affected children in families with autosomal recessive conditions; and e) the lack of public health measures directed at the prevention of congenital and genetically determined disorders, and the shortage of genetic services and inadequate health care prior to and during pregnancy (Al-Gazali et al., 2006; Teebi, 2010, as cited in Teebi, 2010). Thus, in Arab populations, several recessive diseases like Cystic Fibrosis, Phenylketonuria, Beta Thalassemia and Wilson disease are very frequent. However, due to the tribal society style life among Arab and consecutive genetic founder effects, the distribution of autosomal recessive disorders among the Arab populations is not uniformly distributed, but shows large geographic differences (Teebi & S.A. Teebi 2005; Zolotogora 2002).

Consanguinity has been recognized as the main social factor related to a high prevalence of genetic and congenital disorders in Arab communities' worldwide (Bener et al., 2007; Bittles

& Hamamy 2010, as cited in Teebi, 2010; Jaber et al., 1992; Sharkia et al., 2010; Zlotogora, 1997). Consanguineous marriage refers to a union contracted between biologically related individuals. In clinical genetics, this includes relationships of second cousins or closer (Bittles & Hamamy 2010, as cited in Teebi, 2010). The phenomenon of consanguineous marriages has been common in different societies worldwide, especially in the Arab rural populations due to socio-cultural factors like maintenance of family structure, and properties or ease of marital arrangements (Alper et al., 2004; Qidwai et al., 2003; Varela et al., 2003). The prevalence of consanguineous marriages in the Arab world is considered to be much higher (35% - 55%) as compared to Western countries (~1%) (Bittles, 2001; Jaber et al. 1998). Recently, different studies of various Arab societies have shown that the consanguinity rates decrease with time (Hamamy et al., 2005; Khat, 1988; Sharkia et al., 2008). Consanguinity rates in various societies were found to be dependent on multiple factors e.g. religion, educational level, local traditions socio-economic status and demography (Fuster & Colantonio, 2004; Jaber et al., 1996,). The Arab population of Israel reaches about 1.5 million people consisting of about 84 % Muslims, 8 % Christians and 8% Druze (Central Bureau of Statistics, 2010). The Arab community in Israel is characterized by some unique features: most of the population lives in villages or towns which were founded by small numbers of originators and the majority of families have a large number of children. It was also believed that the favorite marriage is the consanguineous one (Jaber et al., 2000). It was found that the frequency of consanguineous marriages in the Arab society in Israel is about 44% (half of which are first cousin marriages) and its incidence is highest in rural areas (Jaber et al., 1994). Consanguinity was recently found to have decreased (Sharkia et al., 2008), in selected Arab communities in Israel but its rate is still high as compared to western communities.

The relationship between consanguineous marriages, inherited genetic diseases and congenital malformation has been studied for many decades. During the 1950s in Japan, a high frequency of infant mortality was associated with consanguinity (Schull, 1958). A study that focused on the consanguinity effects on common adult diseases among the Qatari population revealed a strong correlation between high rates of common adult diseases and consanguineous marriages (Bener et al., 2007). In another study which explored the genetic aspect of beta-Thalassemia among 130 inflicted families from the West Bank and Gaza, 77.3% of the tested couples were found to carry the same mutation. Actually, 77.9% of these couples were from consanguineous marriages (Ayesh et al., 2005). Furthermore, the high rate of infant mortality among the Palestinian population was related to consanguineous marriages (Pedersen, 2002). It was found that consanguineous marriages were a major cause of congenital malformation among the Arab communities in Israel (Jaber et al., 1992). Various forms of congenital malformation of the central nervous system, speech and infertility were found at a higher frequency in those individuals whose parents are family-related, than those with unrelated parents (Bromiker et al., 2004; Zlotogora, 1997). A high proportion of infant mortality due to congenital malformation in the Arab community in Israel is mainly caused by the high frequency of consanguineous marriages (Zlotogora et al., 2003). A report published by Abu-Rabia & Maroun (2005) showed that consanguinity negatively affects children's reading abilities. Recently, it was found that the prevalence of neurological hereditary diseases and mental retardation was associated with consanguinity in selected samples of Arab communities in Israel (Sharkia et al., 2010). From the geneticist's point of view, consanguineous marriage alleviates genetic diagnostics. One main scientifically useful feature of consanguinity is that it facilitates homozygosity mapping of

disease related genes. The present study was undertaken to determine the prevalence of various genetic and congenital disorders and their association with parental consanguinity in a selected sample of the Israeli Arab community. Investigation of hereditary disorders is vital for improving health care. This can be achieved by identifying and diagnosing their molecular genetic basis, with a view to developing preventative intervention measures aimed at reducing the occurrence of these inherited genetic disorders.

## 2. Subjects and methods

### 2.1 Study population and sample

This research is based on data from the socio-economic survey (SES) conducted by the Galilee Society (GS) and Al Ahali Center in the year 2007. This survey included a sample of 3,173 households. This sample was a stratified multi-stage random sample which was designed in three stages: selection of enumeration areas in one stratification level, selection of thirty responsive households in the chosen enumeration area and selection of two persons, male and female, from persons aged 10 years and above from each household that was chosen in the second stage. The total rate of completed questionnaires in this survey was 81.9% of the households in the field.

This sample was divided into four levels of stratification: Region (North, Center, Haifa and South), Community Classification (urban communities "A" with a population over 15,000 and urban communities "B" with a population between 5,000 and 15,000, rural communities with a population less than 5,000), Locality Type (unrecognized and recognized by the Israeli authorities), and Locality Characteristics (mixed: Arabs and others, unmixed: Arabs only).

The following criteria were used in calculating the sample size: Use of the unemployment indicator (rate of unemployment) as a principal indicator in defining the margin of error which was estimated according to previous data at around 12%, Period of confidence is 95%, The ultimate margin of error for the principal indicator (rate of unemployment) is 3% on the stratification level.

Therefore the size of the stratification level is:

$$n_h = \frac{t^2 S^2 D}{e^2} \quad h = 1, \dots, 18$$

$n_h$  the number of persons in one stratification level

$$S^2 = p(1-p)$$

$p$  is the rate of prevalence of the principal feature studied in the survey (unemployment)

$t$  is the confidence factor that expresses the period of confidence

$e$  is the ultimate margin of error in estimating the indicator

$D$  is the effect of sample design of multi-stage stratified samples and is estimated at 1.2.

The result is that the number of persons in one stratification level equals to 564 persons:

$$n_h = \frac{(4)(0.12)(0.88)(1.2)}{(0.03)^2} = 564$$

Since we are covering 18 true levels, the number of persons (N) in the sample in all levels is 10,152 persons

$$N = 564 * 18 = 10152$$

It is important to note that the required number of persons applies to persons in the labor force because the principal feature that was studied (unemployment) is only related to persons in the labor force. Since the sample selection was households, and not persons, therefore we had to choose a number of households which included approximately 10,152 persons in the labor force. According to previous data, the number of persons in the labor force is on average 3.2 persons per household, thus the sample size becomes 3,173 households. Since 30 responsive households were selected from each enumeration area, the required number of enumeration areas was 107.1 and was adjusted to 109 areas, i.e. 3,173 households in order to correlate the enumeration areas with the different levels of stratification.

The target population consisted of all Israeli Arab households that reside inside the green line, and focused on individuals aged 15 years and above during 2007. The study group comprised the full pediatric population (0-18 year old), that was affected with one or more types of disorders caused by congenital, illness or during birth cause. The sample excluded children with disorders caused by accidents or environmental factors. The total number of the study group was 565 affected children.

## 2.2 Survey questionnaire and data collection

For the current study we used two parts from the general questionnaire that contained:

- a. Identification information for the household and the relationship of the household to its head, gender, age, religion and place.
- b. Personal status information: included marital status, whether husband and wife are related, and the degree of consanguinity, and the number of births for married women.
- c. Health status information: included incidence of chronic diseases, disabilities, kinds of disabilities, and causes of disabilities, availability of supplementary health insurance, and places of treatment.

The response compliance rate was 81.0% of the total households who were visited in the enumeration areas where refusals were recorded.

Questionnaires were completed through face to face interviews. The fieldwork team was recruited from a group of field experienced surveyors. A training course was conducted for these surveyors by the supervisors and the project administrators. The total rate of completed questionnaires in this survey was 82% of the households in the field, which was a total of 107 areas out of 109.

## 2.3 Consanguinity

Information on consanguinity between the parents was obtained through the interviews. Relationships were grouped into two major categories: consanguineous and non-consanguineous marriages, defined as follows:

Consanguineous marriage: This group included two main levels of relationships:

- a. First cousins and closer. These include double-first cousins (in which all grandparents are shared) and first cousins in which the couple are parallel or cross cousins of either paternal or maternal descent;
- b. Distant relative marriages, in which the members of the couple were relatives but not with first-degree relations, for example they were first cousin once removed, second cousin, second cousin once removed.

Non-consanguineous marriage: The couple is not related.

## 2.4 Data analysis

The SPSS program was used for data management and descriptive statistical analysis. The statistical significance of associations between consanguinity and various types of disorders was examined by means of the  $\chi^2$  test.

## 3. Results

Of 3,173 total marriages (households), 1267 (39.9%) were consanguineous and 1906 (60.01%) were non-consanguineous. The various subtypes of consanguinity was observed; 19.7% (N=623) were first-cousin marriage type and a similar incidence was found for distant relative marriage type (N=644, 20.3%). Of the 6,017 total children (siblings) from all the family samples, 565 children were found to have one or more kinds of various types of disorders, comprising an overall prevalence of 93.9 per 1000 children sampled.

The total numbers of affected children of varying degrees separated into those from consanguineous and from non-consanguineous marriages are presented in Table 1. More than half of affected children (56%) were found to be products of parental consanguinity; 68.4% of this prevalence was offspring of first cousins or closer, and 31.6% were offspring of distant relatives. About 44% of the affected children were born to unrelated couples. There was a significant difference in the prevalence between the offspring of consanguineous versus non-consanguineous mating for various types of examined disorders. All reported disorders were more frequent in consanguineous marriages, except for the respiratory disorders which were more frequent in non-consanguineous marriages, indicating that there is a significant association between consanguinity and types of disorders, and that genetic factors are probably the underlying cause.

Type of disorders	Number of affected children	Consanguineous n (%)			Non-consanguineous n (%)	$\chi^2$	P
		Total	FC	DR			
Respiratory	130	56 (21.5)	32 (57.1)	24 (42.9)	74 (78.5)	16.6	0.003
Mental	53	28 (52.8)	19 (67.8)	9 (32.2)	25 (47.2)	14.03	0.002
Physical	160	90 (56.3)	68 (75.5)	22 (24.5)	70 (43.7)	13.25	0.001
Visual	100	66 (66)	47 (71.2)	19 (28.8)	34 (34)	15.2	0.0013
Hearing	77	51 (66.2)	36 (70.5)	15 (29.5)	26 (33.8)	6.06	0.0020
Other Hereditary Disorders	45	25 (55.5)	14 (56)	11 (44)	20 (45.5)	18.41	0.000
Total	N=565	316 (56%)	216 (68.4)	100 (31.6)	249 (44%)	17.98	0.000

Table 1. Distribution of disorder types among Offspring from Consanguineous and Non-consanguineous Marriages

Table 2 records the numbers and prevalence of disorder types among all the siblings aged 0 to 18 in the presented families. The data shows that approximately 31% (565 cases) of the siblings from all 356 families had one or more kinds of diseases with a prevalence range of 22% to 40%. This indicates that there is an associated familial background. Selected characteristics of affected children with disorders types are presented in Table 3. The prevalence of disorders' types was higher in boys (60%) than in girls (40%), this difference was significant. The detailed age distribution recorded in the table shows that the most (70%) of affected children were in the 10 to 18-year age group.

Types of disorders	Number of families	All siblings aged between 0 and 18 years in the families	Number and percentage of affected children (%)
Respiratory	70	420	130 (30)
Mental	33	132	53 (40)
Physical	89	445	160 (35.9)
Visual	92	460	100 (21.7)
Hearing	41	205	77 (37.5)
Other Hereditary disorders	31	155	45 (29)
Total	356	1817	565 (31.9)

Table 2. Number and percentage of affected children from of all children siblings in the families

Age (years)	Affected children with disorders' types						Total Affected children N (%)
	Respiratory	Mental	Physical	Visual	Hearing	Other Hereditary disorders	
< 5	30 (32.6)	9 (9.7)	20 (21.7)	9 (9.7)	19 (20.6)	5 (5.4)	92 (16.2)
5-10	15 (19.7)	7 (9.2)	19 (25)	17 (22.3)	15 (19.7)	3 (3.9)	76 (13.4)
10 -15	19 (17.7)	15 (14.1)	26 (24.2)	28 (26.1)	12 (11.2)	7 (6.5)	107 (19)
>15	66 (22.7)	22 (7.5)	95 (32.7)	46 (5.8)	31 (10.6)	30 (10.3)	290 (51.4)
Gender							P<0.05 sig=0.01
Male	80 (23.5)	33 (9.7)	107 (31.5)	56 (16.5)	38 (11.2)	25 (7.3)	339 (60)
Female	50 (22.1)	20 (8.8)	53 (23.4)	44 (19.4)	39 (17.2)	20 (11.1)	226 (40)
Total	130 (23)	53 (9.3)	160 (28.3)	100 (17.6)	77 (13.6)	45 (7.9)	565 (100)
							P<0.05 sig=0.00

Table 3. Age and Gender of affected Children with disorders' types

Table 4 compares the prevalence of disorders' types among the offspring from three category causes of disorders: illness, congenital and during birth. Most (97%) of the disorders causes among affected children were illness and congenital. The illness cause was recorded in 300 cases (53.2%) and in 251 cases (44.4%) there was a congenital cause. Only 14 cases (2.4%) were caused by "during birth".

Cause of Disorder	Children with types of disorders						
	Respiratory diseases	Mental disorders	Physical disorders	Visual disorders	Hearing disorders	Other Hereditary disorders	Total N (%)
Illness	81 (62.3)	13 (24.5)	101 (63.1)	52 (52)	28 (36.3)	25 (55.5)	300 (53.2)
Congenital	48 (36.9)	37 (69.8)	57 (35.6)	45 (45)	46 (59.7)	18 (40)	251 (44.4)
During birth	1 (0.8)	3 (5.6)	2 (1.2)	3 (3)	3 (3.8)	2 (4.4)	14 (2.4)
Total	130	53	160	100	77	45	565

Table 4. Frequency of disorders' types by cause of disorders

#### 4. Discussion

The highest prevalence of congenital malformations and genetic diseases was reported in the Eastern Mediterranean region, with >65 affected children per 1,000 live births as opposed to 52/1,000 live births in Europe, North America and Australia (Alwan & Modell, 2003). In the selected sample for the present study we found that various types of disorders affected, on average, 93.9 per 1000 children. This finding indicates that morbidity in the studied population is considerably more prevalent than in Eastern Mediterranean regions as well as in western societies.

The phenomenon of consanguineous marriages has been common in the Arab world for many decades and its prevalence is considered to be much higher (35% - 55%) as compared to that (~1%) of Western countries (Bittles, 2001; Jaber et al., 1998; Tadmouri et al., 2009). Nevertheless, despite the previously reported decrease in the rate of consanguineous marriages within selected regions of Israeli Arab communities (Sharkia et al., 2008), the consanguinity rate is still high in this community as the current study indicates. Our study, which is based on data obtained from all regions of the Israeli Arab community, showed that the incidence of consanguinity is relatively high with a rate of about 40%. Approximately 50% of all these consanguineous marriages are of the first-cousin and closer marriage type. These findings can be explained by the preference of consanguineous marriages in Arab populations that are related to socio-cultural factors. It has been reported that consanguineous marriages have a negative effect on reproductive health factors in general. Consanguinity is still the most common risk factor for a high frequency of autosomal recessive diseases and congenital malformations within Arab communities in Israel (Sharkia et al., 2010; Zoltogora et al., 2003). In addition, several studies among Arab societies show that there is a higher occurrence of consanguineous marriages among parents of offspring with congenital malformations than in the general population (Bener et al.,

2007; Tadmoure et al., 2009; Teebi, 2010, as cited in Teebi, 2010). A strong association between most of the examined disorders and consanguinity was demonstrated in the present study; approximately 56% of the children with one or more disorders were the offspring of consanguineous marriages, and in approximately 68% of these marriages the parents were first cousins or closer. This association between consanguinity and disorder rate as well as the familial effect of most disorders' types that were obtained by the current results indicate that genetic factors are involved with the underlying cause. In addition, we found that the frequency of the disorders' types were higher among males (60%) than females (40%) in our studied sample, possibly reflecting the elevated levels of X-chromosome homozygosity inheritance. The relationship between consanguinity and genetic disorders is attributed to the fact that a high prevalence of consanguinity increases homozygosity and reduces the genetic variation which may protect against the expression of recessive genes that can lead to genetic disorders in a group. When a new mutation is inserted in such a population, it will rapidly spread, leading to an increased prevalence of carriers, and a high number of affected homozygous individuals. An analysis of data in the Catalogue for Transmission Genetics in Arabs (CTGA) carried out by Tadmouri et al., (2009), indicates that the overwhelming proportion of the disorders follow a recessive mode of inheritance of about 63% as compared to the smaller proportion of dominantly inherited traits (27%). A detailed analysis study of the molecular basis of autosomal recessive diseases among Palestinian Arabs in Israel found that most of the responsible mutations among the affected patients were homozygosity (Zlotogora, 2002). We believe that the genetic conditions of the disorders in the present studied sample probably relates to homozygosity autosomal recessive diseases.

The largest age distribution (70%) of affected children was in the 10 to 18-year range, in contrast to the 16% of affected children who were in the less than 5 year age group. Furthermore, most (97.6 %) of the disorders causes among the affected children were by illness and congenital, while only (2.4%) were caused by "during birth". These results demonstrated that implementing various health interventions and genetic counseling services in order to improve public health issues in the Israeli Arab community will have a positive effect, even if only partial. Therefore, such programs are needed, particularly, for identifying and diagnosing the molecular genetic basis of the most common disorders so that a preventive program can be launched, with the aim of minimizing the occurrence of different spectrum disorders in future generations.

## 5. Acknowledgements

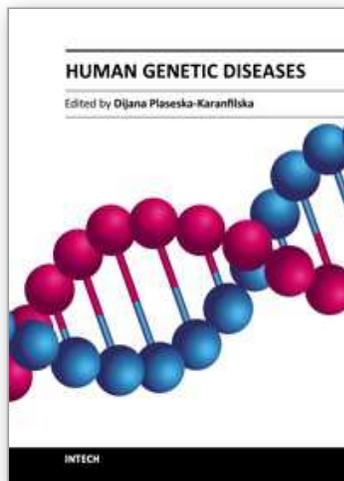
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## **Human Genetic Diseases**

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The genetics science is less than 150 years old, but its accomplishments have been astonishing. Genetics has become an indispensable component of almost all research in modern biology and medicine. Human genetic variation is associated with many, if not all, human diseases and disabilities. Nowadays, studies investigating any biological process, from the molecular level to the population level, use the “genetic approach” to gain understanding of that process. This book contains many diverse chapters, dealing with human genetic diseases, methods to diagnose them, novel approaches to treat them and molecular approaches and concepts to understand them. Although this book does not give a comprehensive overview of human genetic diseases, I believe that the sixteen book chapters will be a valuable resource for researchers and students in different life and medical sciences.

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Phone: +86-21-62489820  
Fax: +86-21-62489821

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